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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	A-68104/DJB/	5176

959 7590 03/26/2004

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-16 have been cancelled.

Claims 17-20 are under examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility for reasons set forth in the last Office action.

Response to Arguments

In view of the cancellation of claims 1-16, the rejection is moot.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

> use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons set forth in the last Office action.

In view the cancellation of claims 1-16, the rejection is moot.

Claims 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide enablement for a method using a library of any bioactive agents or nucleic acid that encodes said bioactive agents that modulates any population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons advanced in the last Office action.

Response to Arguments

Applicants argue that the specification clearly describes what is meant by candidate bioactive agent giving examples of the types of candidate agents, describing categories of

candidate agents, properties of candidate agents, sources of candidate agents, methods of obtaining or producing candidate agents, and modifications of candidate agents using a variety of fusion partners for a variety of purposes (see, e.g., the specification at page 16, line 10 to page 30, line 15).

Applicants submit that it would be clear to one of skill that the method steps of contacting the candidate bioactive agent to a cell (e.g., tumor cell or other), sorting a cell by FACS, and screening a cell on the basis of at least five parameters, does not require limiting the scope of the claims based on the description set forth in the specification, much less limiting the claimed method to the use of p21. Rather, the method steps provide for the use of a wide variety of candidate bioactive agents as set forth in the specification. Moreover, Applicants point out that strength of the invention is that a library of candidate agents can be-tested for an ability to alter cellular phenotype. (Specification, for example, at page 31, line 30). Thus, a particular candidate agent need not be known to be effective with regard to altering cellular phenotype in order for the agent to be used in the claimed methods. The invention can be practiced with a mixture of known or unknown agents (for

example a library comprising such a mixture) and can be used to elucidate bioactive agents that can alter cellular phenotype. Accordingly, Applicants submit that enablement of the use of candidate agents other than p21 does not require teaching methods for first identifying agents that have phenotype altering activity. Regarding the use of cell types other than tumor cell types in the screening methods, Applicants direct the Examiner to page 9, lines 14-1 7 and page 1 0, lines 10- 1 3 of the specification. The specification clearly describes that a variety of cell types, including mixtures of cell types, are useful in the instant invention. In addition, the Office Action provides no evidence showing that cell types other than tumor cell types could not be contacted with candidate bioactive agents in some way, or that cells so contacted could not be sorted by FACS, and screened on the basis of at least 5 parameters for an alteration in cellular phenotype.

In response, it is not the definition of the candidate bioactive agent that is at issue. Rather, the scope of the candidate agent encoded by a population of retroviral vectors. As stated by applicants above, the candidate bioactive agents include numerous types of agents in the modified and unmodified state. These agents of unknown constitution when made into a library may not provide a true representation of the candidate

agents in the library. It is not therefore apparent from the enabling disclosure which bioactive agent can be considered candidate to affect the cell phenotype. Mere recitation of a method with any agent without knowing how the agent manipulatively affects the cell phenotype entails undue experimentation. There are too numerous undefined variables for one skilled in the art to determine in order to practice the claimed invention. To select and determine the various agents that would affect a cell phenotype in five different ways amounts to an invitation to experiment. Before measurement of even a single effect is achieved, one has to identify the source (agent) that causes the different cellular phenotype parameters. Because the art is so highly unpredictable, specifically the library of bioactive agents such as peptide, carbohydrates, lipids, DNA or combinations thereof, one cannot make prophetic statements, absent experimental studies. Accordingly, to determine the numerous possible combinations of each of the broadly recited parameters encompassed by the claims requires undue experimentation. The claimed invention is nothing more than an invitation to experiment.

[It is suggested that applicants amend the claims to recite a method to the use of library of p21 and its mutants as the bioactive agents in tumor cell populations].

Double Patenting

Claims 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 for reasons of record.

Response to Arguments

Applicants state that at such time as the subject matter of the provisionally rejected claims is allowed in the '330 or '748 applications, Applicants will terminally disclaim the corresponding claims of the present application.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being obvious over Application No. 09/157,748 (now U.S. 6,461,813) which has a common inventor with the instant application for reasons advanced in last Office action.

Applicants request that the rejection be held in abeyance as Applicants prepare to submit a declaration under 132 to show that the relevant disclosure in the '748 patent is not the work of another.

In reply, in the absence of the 132 declaration the rejection is maintained. [Note that the '748 application has matured into a patent].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-20 are rejected under under 35 U.S.C. 103(a) as being obvious over Nolan (WO 97/27212) in view of Kamb for reasons advanced in the last Office action.

Response to Arguments

Applicants argue that Nolan discloses sorting cells on the basis of a single parameter in Example 1 (i.e. the content of fluoresceinated). But admit that Nolan broadly describes methods for isolating a cell having an altered phenotype from the plurality of other cells. FACS and expression of a survival protein are each merely listed as one of a number of methods for effecting isolation. But argue that the list of methods

for effecting isolation has been erroneously interpreted as parameters for screening for an alteration in cellular phenotype. It is further argued that three parameters are inherent to prior art teachings using FACS, namely fluorescence, viability and apoptosis. Applicants assert that the claims do not recite viability and apoptosis as parameters. Specifically, the claims recite phenotypes, including apoptosis. Further, viability is a state which may be determined by sorting cells by FACS on the basis of a described parameter, e.g., dye exclusion. Apoptosis is described as a cellular phenotype in the present invention, and alterations in apoptosis can be screened for by sorting cells by FACS on the basis of parameters including for example dye exclusion. Applicants submit that the prior art of record does not disclose the sorting of cells by FACS and screening on the basis of at least five parameters for the object of screening for an alteration in cellular phenotype.

In reply, as admitted by applicants Nolan provides a list for the effective isolation of bioactive agents that affect cell phenotype. The suggested teaching in the list of Nolan suffices the finding of obviousness. Attention is directed at e.g., Example 1, line 23 up to page 52, line 2 wherein the cells after washing is transferred to Fluorescent activated cell sorting

(FACS) tube for analysis which shows expression of Bcl2(expression of cell surface receptor, as claimed) from retroviral promoter that inhibits apoptosis. FACS machine are known to measure optical properties like (1) fluorescence which would indicate that the cell is (2) viable and that the agent inhibit (3) apoptosis. [Note page 1, lines 26-28 of the instant specification which recites the known fact that FACS is used to sort individual cells on the basis of optical properties, including fluorescence.] See further the disclosure of Nolan at page 33, lines 19-28 wherein Nolan describes that once a cell with an altered phenotype is detected, the cell is isolated from the plurality which do not have altered phenotypes. This is done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include FACS, expression of survival protein, (cell cycle, as claimed) induced expression of a cell surface protein(expression of a cell surface receptor, as claimed) or other molecule that can be rendered fluorescent or taggable for physical isolation, death of cells (apoptosis) and isolation of DNA or other cell viability indicator dyes etc. In Example 1, page 51 uses FACS to analyze a fluoresceinated cell, expression of the cells, apoptosis inhibition, use of dye techniques as

propidium iodide or other dyes such as ethidium bromide/acridine orange.

Kamb, as stated in the last Office action teaches the use of FACS to separate cells based on the expression of a single reporter gene. The population of cells is sorted based on expression of a reporter gene. Kamb refers to GFP as a vital dye that refers to the fact that the GFP is expressed without killing the cell. Kamb discloses the sorting of the single expressed gene by sorting the cells based on the different cellular parameters of (1) a fluorescently labeled antibody (i.e., immunofluorescence); (2) quantifying measurement level of the expressed reporter gene (e.g., col.8, line 45 up to col. 9, line 7) and (3) the uptake of the GFP (a "vital dyes") or its emission or (4) the use of BFP. Therefore, the combined teachings of Nolan and Kamb render the determination of at least 5 cellular phenotype prima facie obvious. It discloses the different known parameters by which cell phenotype alteration can be measured.

Claim 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nolan in view of Kamb and further in view of Hide et al(Jrnl. of Cell Biology) for reasons advanced in the last Office action.

Response to Arguments

Applicants argue that Hide broadly teaches using flow cytometer to sort peritoneal mast cells based on measurement of 90 degrees light scatter. Without addressing the exocytosis disclosure of Hide, Applicants point out that Hide does not teach adding at least four parameters for screening for an alteration in cellular phenotype and, thus, cannot be combined with the teachings of Nolan to teach at least five parameters.

In response, Hide is combined with Nolan and Kamb for the its teaching as to the cellular phenotype, exocytosis and measuring said cellular parameter to detect the forward and light scattering of cells to show the exocytosis effect of the cells. This attribute has been used to classify populations of (mast) cells. Thus, applicants cannot attack the references individually when the rejection is based on the combination of references. One having ordinary skill in the art would have been motivated to measure another cellular parameters as light scattering by FACS when the cellular phenotype is caused by exocytosis to provide a clear or discernible effect of the cells.

It is argued that no evidence has been provided to support the assertion that the combination of the known parameters measured by FACS result in a clear identification of the cells. In reply, each of these references measures the different

parameters to provide a clear identification of the agent causing cell phenotype effect. This is sufficient evidence that the different combinations of measuring these different parameters would lead to a better identification of the affected cell. It is well known the overall performance of the combination is always equal to the sum of the functions of the individual components.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
March 22, 2004